Azixa, a Microtubule Destabilizing Agent, in Solid Tumors: Results of a Phase 1 Trial

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Background

- MPC-6827 (Azixa™; a 4-arylaminoquinazoline) is a small molecule microtubule destabilizing agent that causes mitotic arrest and cell death
- *In vitro*, MPC-6827 displayed proapoptotic activity, with potency at low nanomolar concentrations in a broad spectrum of cancer cells
- In mice, MPC-6827 significantly inhibited the growth of a variety of subcutaneously implanted tumor lines.
- MPC-6827 has also been shown to be a vascular-disrupting agent (VDA) in a human ovarian OVCAR-3 carcinoma xenograft
- VDAs have been established to reduce interstitial pressure in the tumor microenvironment, which may increase local exposure to cytotoxic chemotherapy

Patients and Methods

- Patients with advanced or metastatic cancer were treated with once-weekly intravenous (IV) infusion for 3 weeks every 28 days
- Dose escalation began with 0.3, 0.6, 1, and 1.5 mg/m^2
- Subsequent increments of 0.6 mg/m^2 were given until the MTD was determined
- A conventional "3 + 3" design was used
- Responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST)

Definition of DLT

- ≥ Grade (G) 3 nonhematologic toxicity (excluding nausea/vomiting or alopecia)
- ≥ G3 nausea/vomiting uncontrolled by aggressive antiemetic support
- G4 neutropenia lasting > 5 days
- Any febrile G3- 4 neutropenia
- G4 thrombocytopenia or
- ≥ G2 neurologic toxicity without resolution within 72 hrs

Pharmacokinetics

- Plasma concentrations of MPC-6827 and its O-demethyl metabolite, MPI-0440627 were determined after the first and third IV infusions during cycle 1 (i.e. on study days 1 and 15). Blood samples were collected before MPC-6827 administration, at the end of drug infusion, and at 1, 2, 4, 6, 12, and 24 hours post-infusion

Antitumor activity

- All subjects underwent a CT scan or MRI at screening, at Day 28 ± 7 days, and every 28 ± 7 days thereafter until the end of the study, and at the final visit

Patient Characteristics (N=48)

Characteristic	No. of pts	%
Age (years)		
Median	56	
Range	26-76	
Age ≥ 60 years	18	38
Gender		
Male	26	54
Female	22	46
Karnofsky PS		
100	12	25
90	5	10
80	29	60
70	2	4
No. of prior therapies		
Median	5	
Range	1-12	
No. of patients with brain mets	10	21
Type/site primary cancer		
Lung	8	17
Melanoma	7	15
Colon	6	13
Breast	4	8
Ovarian	3	6
Pancreas	3	6
Prostate	3	6
Renal cell	2	4
Other*	12	25

* Adenoid cystic (n=1), bronchoalveolar (n=1), endometrial (n=1), follicular dendritic (n=1), gastroesophageal adenocarcinoma (n=1), large cell carcinoma (n=1), Merkel cell carcinoma (n=1), mesothelioma (n=1), mucoepidermoid carcinoma (n=1), parathyroid (n=1), thymoma (n=1), and tonsillar (n=1)

Distribution of Pts, Cycles, and DLTs

Dose mg/m^2	No. of pts	Site		No. of Cycles	No. of pts. with DLTs	Description of DLTs
		MDACC	Huntsman			
0.3	3	3		3-5	0	
0.6	3	3		1-2	0	
1.0	3	3		1-3	0	
1.5	7	6	1	1-5	2	G4 hypersensitivity, G3 dyspnea
2.1	3	2	1	1-2	0	
2.7	3	2	1	1	0	
3.3	13	11	2	1-4	0	
3.9	6	4	2	1-2	1	G3 myocardial infarction
4.5	7	5	2	1-10	1	G3 myocardial infarction

Parameters for MTD

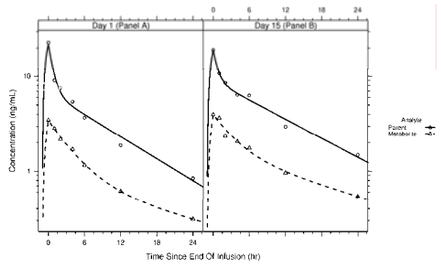
Day & Analyte	Redistribution $t_{1/2}$, α hr	Terminal $t_{1/2}$, β hr	C_{max} ng/mL	$AUC_{(0\text{-}inf)}$ hr*ng/mL
Day 1, MPC-6827 (parent)	0.16	15.10	22.83	99.66
Day 15, MPC-6827			19.11	144.70
Day 1, MPI-0440627 (metabolite)	12.90		3.56	54.53
Day 15, MPI-0440627	11.43		4.24	49.92

Mean Parameters for MTD of 3.3 mg/m^2, C_{max}, and AUC $_{(0\text{-}\ )}$

Adverse Events (I)

Dose, mg/m^2	0.3 n=3		0.6 n=3		1 n=3		1.5 n=7	
NCI-CTCAE Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
Hypersensitivity								2
Hyperglycemia	3						1	
Flushing	6		3				5	
Hot flush							2	
Fatigue	2						4	
Nausea					1		1	
Vomiting								
Headache			3				1	
Elevated AST							3	
Elevated ALT							4	
Elevated alkaline phosphatase							7	
Dyspnea								1
Myocardial infarction								
Bradycardia								
First degree AV block								
Hypertension								
Edema								
Chest pain								
Abdominal pain								
Back pain								
Skin pain								
Myalgia								
Pain in extremity								
Pain					1			
Anemia								
Insomnia								
Arthralgia			1					
Mucosal Inflammation			1					
Pruritus								
Anorexia							1	
Anxiety								
Pyrexia								

Parent and Metabolite Concentrations



MPC-6827 (parent) and MPI-0440627 (metabolite) mean concentrations for patients treated at the MTD of 3.3 mg/m^2. Panel A shows the Day 1 treatment, and Panel B shows Day 15 treatment. Parent mean concentrations are shown with circles, while metabolite concentrations are shown with triangles. The best fit line for parent is a solid line, while the best fit for metabolite is a dashed line.

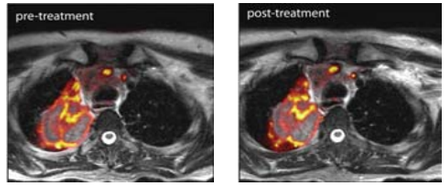
Adverse Events (II)

Dose, mg/m^2	2.1 n=3		2.7 n=3		3.3 n=14		3.9 n=6		4.5 n=6	
NCI-CTCAE Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
Hypersensitivity										
Hyperglycemia			1		1		1		1	
Flushing					1		1		1	
Hot flush										
Fatigue					5		1		1	
Nausea					1		1			
Vomiting							1			
Headache					1					
Elevated AST										
Elevated ALT										
Elevated alkaline phosphatase										
Dyspnea									1	
Myocardial infarction								1		1
Bradycardia							2			
First degree AV block									1	
Hypertension					9		1			
Edema							1			
Chest pain									1	
Abdominal pain							2			
Back pain							2			
Skin pain							1			
Myalgia									1	
Pain in extremity					1					
Pain										
Anemia									1	1
Insomnia	1									
Arthralgia										
Mucosal Inflammation										
Pruritus			1							
Anorexia					1					
Anxiety					2					
Pyrexia					1					

Stable Disease (N=5)

Age/ Sex	PS	Dose, mg/m^2	No. of Cycles	Type of Cancer	No. of Prior Therapies	Prior Therapies
64/F	100	0.3	5	Breast	11	Tamoxifen, anastrozole, estramustine, Fasldex, doxorubicin, gemcitabine, Xeloda, paclitaxel, 5-FU + cyclophosphamide + adriamycin, TAS-102, CRX-026
41/F	80	1.5	5	Endometrial	3	Medroxyprogesterone acetate, paclitaxel + carboplatin, tamoxifen + Arimidex
58/M	90	3.3	10	Carcinoid of the rectum	3	Bevacizumab, bevacizumab + erlotinib, AMG-386
50/M	80	3.3	4	Thymoma	5	Cyclophosphamide + adriamycin + cisplatin, Taxotere + carboplatin, carboplatin, azacitidine + valproic acid, RTA402
47/F	80	4.5/3.3	5	Parathyroid	2	MST-997 + zoledronic acid, docetaxel + zoledronic acid + cinacalcet hydrochloride

DCE-MRI



Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) maps of K^{trans} in a patient with a large primary non-small cell lung cancer of the right apical lung

Conclusions

- MPC-6827 was well tolerated up to and including the MTD of 3.3 mg/m^2 IV once weekly x 3
- Myocardial infarction was the DLT at 3.9 mg/m^2 and 4.5 mg/m^2
- MPC-6827 exhibited two-compartment kinetics with a short redistribution phase and a slower terminal elimination
- Five heavily pre-treated patients had stable disease for ≥ 4 months

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